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Health and Environmental Effects Profile for Captafol

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16. ABSTRACT

The Health and Environmental Effects Profile for captafol was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Captafol has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for captafol is 8.6×10^{-3} (mg/kg bw/day)$^{-1}$ for oral exposure.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CAPTAFOL

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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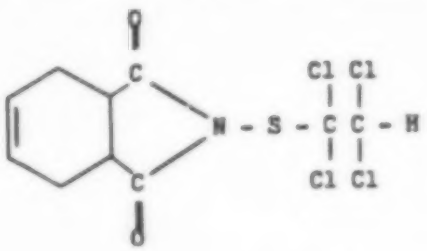
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
DNA	Deoxyribonucleic acid
EC_{50}	Concentration effective for 50% of recipients
FEL	Frank-effect level
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
SCE	Sister-chromatid exchange
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Captafol is the common name for 3a,4,7,7a-tetrahydro-N-(1,1,2,2tetrachloroethanesulfenyl)phthalimide. Current Chemical Abstract usage is 3a,4,7,7a-tetrahydro-2-(1,1,2,2-tetrachloroethyl)thio-1H-isoindole-1,3(2H)-dione and was formerly N-[(1,1,2,2-tetrachloroethyl)thio]-4-cyclohexene-1,2-dicarboximide. Other chemical synonyms include N-tetra-chloroethylthio-1,2,3,6-tetrahydrophthalimide and tetrachloroethylmercaptocyclohexenedicarboximide. It was introduced in 1961 by the Chevron Chemical Company under the trade mark "Difolatan" (Martin and Worthing, 1977). Other trade names include "Difosan," "Folcid," "Ortho 5865," "Sanspor" and "Sulfonimide." The structural and empirical formulae for captafol are as follows:



The empirical formula for captafol is $C_{10}H_9Cl_4NO_2S$ and the molecular weight is 349.1. The Chemical Abstract Service (CAS) Registry number is 2425-06-1.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Captafol is a white crystalline solid (Martin and Worthing, 1977). Selected physical properties are listed below:

Melting point:	160-161°C with slow decomposition (Martin and Worthing, 1977)
Vapor pressure:	negligible at room tempperature (Martin and Worthing, 1977)

Water solubility:	1.4 mg/ℓ (Martin and Worthing, 1977)
Bioconcentration factor: (calculation from water solubility)	510 (Kenaga, 1980)
Soil sorption coefficent: (calculation from water solubility)	3600 (Kenaga, 1980)
Log octanol/water partition coefficient	3.83 (Briggs, 1981)

Captafol hydrolyzes in water to 50% of its original concentration in 150 minutes at a pH of 7 and 28°C (Wolfe et al., 1976a). It decomposes slowly at its melting point and is compatible with most pesticides (Martin and Worthing, 1977). It is slightly soluble in organic solvents (Spencer, 1968).

1.3. PRODUCTION DATA

Captafol is prepared by the reaction of the imide, formed by action of ammonia on tetrahydrophthalic anhydride, with 1,1,2,2-tetrachloroethyl sulfenyl chloride (Martin and Worthing, 1977).

The only domestic producer of captofol is Standard Oil of California (Chevron Chemical) in Richmond, CA (SRI, 1983; USITC, 1983). Current production figures are not available. The capacity of Chevron's plant is reported to be 2 million lb/year (SRI, 1976).

1.4. USE DATA

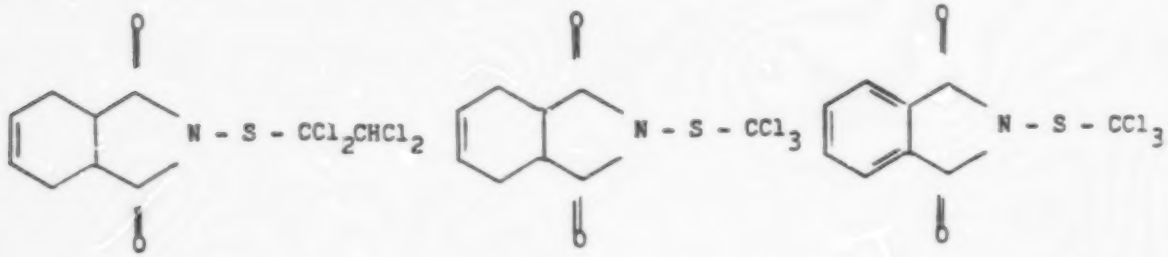
Captafol is a protective nonsystemic fungicide used for control of foliage and fruit diseases of tomatoes, potato blight, coffee berry disease, tapping panel disease of Hevea and control of diseases of other agricultural, horticultural and plantation crops (Martin and Worthing, 1977). It is also used in the lumber and timber industries to reduce losses from wood rot fungi in logs and wood products (Martin and Worthing, 1977). Suggested application rates are 200 g active ingredient/100ℓ water (Martin and Worthing, 1977) or 2 lb/100 U.S. gallons (Spencer, 1968).

In 1976, American farmers used 169,000 pounds of captafol on peanut crops (Eichers et al., 1978). In 1977, 384,949 pounds of captafol were used on Florida citrus (Haydu, 1981), while in 1978 in the United States (excluding California) 69,700 pounds were used on tart cherries and 243,100 pounds were used on apples (Webb, 1981). In 1979, 186,900 pounds of captafol were used on fall potatoes (Parks, 1983) in the United States.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

As with other chemicals, the fate of captafol in water will depend on its ability to undergo chemical, photochemical and biological reactions and partition into the atmosphere or adsorb to sediments. Wolfe et al. (1976a) have suggested that hydrolysis is likely to be the predominating pathway of degradation of captafol in the aquatic environment, due to its rapid degradation rate in water. Using a buffered pH range (7.0-7.2), Wolfe et al. (1976a) found that degradation half-lives of the fungicides captafol, captan and folpet followed apparent first-order reaction kinetics, with rate constants at 28°C as $7.7 \times 10^{-5} s^{-1}$, $6.5 \times 10^{-5} s^{-1}$ and $1.4 \times 10^{-4} s^{-1}$, respectively. The chemical structures of these fungicides (as shown below) suggest similar hydrolysis rates.



Captafol Captan Folpet

The hydrolysis half-lives of captafol, captan and folpet, using the apparent first-order rate constants above, are 150 minutes, 178 minutes and 83 minutes, respectively. The same experiment was conducted with natural water from the Tombigbee River in South Carolina (pH=7.0) for captan; the calculated halflife was 155 minutes, which is in good agreement with the previously calculated 170 minutes. Additionally, Wolfe et al. (1976a) measured the hydrolysis rate of captan over the pH range of 2-9. From pH 2-6, the

hydrolysis half-life was ~11 hours, but decreased rapidly thereafter until a half-life of 10 minutes was reached near a pH of 9. The pH-hydrolysis profile for captafol may be similar, although this determination has not been investigated.

The photodegradation of captafol has not been adequately studied. Serra (1964) has reported that the degradation of captafol, captan and folpet by UV irradiation was as follows: folpet < captan < captafol. A captan film was exposed to sunlight for 8 hour/day and was degraded 17, 30, 51 and 62% at the end of the first, second, third and fourth days, respectively. The effect of direct photolysis of captan, employing a light that was 80 times more intense than sunlight, was studied by Wolfe et al. (1976b); it was concluded that the direct photolysis rate of captan is not able to compete with its hydrolysis rate. However, Wolfe et al. (1976b) found that the photosensitized oxygenation of captan may be important and suggested that captafol may be photo-oxidized in a similar fashion. Wolfe et al. (1976b) have concluded from the available data that captan hydrolysis is probably more rapid than photoxidation in natural waters.

Data specific to the microbial degradation of captafol in aquatic media could not be located in the available literature.

The transport of captafol, either by adsorption to sediment or volatilization from water, has not been studied. Data discussed in Section 2.3. predict that captafol may be tightly sorbed in soils; therefore, sorption to sediment may be an important process in water systems.

Kenaga (1980) has predicted a BCF, based upon water solubility, for captafol to be 510. This indicates that captafol may not be strongly bioconcentrated. However, the measured log octanol-water partition coefficient

of 3.83 (Briggs, 1981) indicates that captafol may be strongly bioconcentrated. Experimentally determined BCFs are not available from the literature.

2.2. AIR

Data specific to the fate and transport of captafol in the air could not be located in the available literature.

2.3. SOIL

The fate and transport of captafol in the soil have received very little study. As noted in Section 2.1., captafol undergoes rapid hydrolysis in water; therefore, it may be likely that captafol will hydrolyze significantly in moist soils.

Wolfe et al. (1976b) examined the sensitized photoxidation of captan in various water conditions and noted that captafol may be oxidized in a similar fashion. While noting that captan degradation due to photoxidation is not as rapid as degradation due to hydrolysis in natural waters, Wolfe et al. (1976b) suggested that photoxidation of captan on leaf, fruit or soil surfaces may be important. This may also be true for captafol.

Data specific to the microbial degradation of captafol in soils could not be located in the available literature.

Kenaga (1980) has predicted the soil sorption coefficient (K_{oc}) for captafol, based upon its water solubility, to be 3600. Compounds having a K_{oc} value of 1000 or higher are quite tightly bound to organic matter in soil and are considered immobile (Kenaga, 1980). Briggs (1981) measured an adsorption coefficient (K_{oc}) of 1202, which confirms the strong adsorption of captafol to soil and sediments.

Volatilization from soil can be inversely related to soil sorption. As noted above, soil sorption is probably quite high; therefore, captafol volatilization from soil may be very low.

The overall persistence of captafol in soil is not available; however, Fo:chi et al. (1970) have suggested that captafol is degraded rapidly in soil. Neely (1970) field tested the persistence of captafol on 12 types of wood and leaves during a dry summer in Illinois and found an average persistence of 4-6 weeks.

3. EXPOSURE

3.1. WATER

Only one individual water sample has reported captafol monitoring levels in the U.S. EPA STORET Data Base. This whole water (water plus sediment) sample was taken on May 7, 1974, from the lower Salinas River in Monterey, CA; the captafol concentration was 0.09 µg/l.

Additional monitoring data for captafol in water could not be located in the available literature.

3.2. FOOD

McLeod et al. (1980) have monitored Canadian food in a national survey to determine pesticide residues in the total diet. Food samples representing 11 classes of food were collected from five Canadian regions. Monitoring for captafol was done with a minimum detection limit of 5 ppb; no captafol was detected.

The FDA has monitored American foods for pesticide residues during the Total Diet Program and during the FDA Monitoring Program. The Total Diet Program analyzed ready-to-eat food composites obtained from ~30 cities annually, while the Monitoring Program examined raw agricultural commodities, both domestic and imported. During the fiscal years 1970-1976, only one positive detection for captafol was made in each of the following food groups: processed foods, processed fruit products and vine and ear vegetables. Four positive detections were made in small fruits (Duggan et al., 1983).

In abstracts from foreign studies, Bencivenga et al. (1980) detected captafol and other pesticides in very small amounts (trace-1.80 ppm) in table grapes grown near Rome, Italy. Martens and Zenon-Roland (1973) found captafol residues on lettuce at harvest time in Belgium, but noted that

levels varied with rainfall and that, in many cases, the lettuce was completely washed of captafol by rain. Soda et al. (1979) found captafol residues in some Japanese foods.

3.3. INHALATION

Monitoring data for captafol exposure in the atmosphere could not be located in the available literature.

3.4. DERMAL

Monitoring data for captafol exposure on the skin of American workers could not be located in the available literature.

4. PHARMACOKINETICS

In mutagenicity studies (Moriya et al., 1976, 1978, 1983; Rocchi et al., 1980), captafol was inactivated by incubation with the S-9 liver fraction, with cysteine or with blood or serum (Section 5.2.). It was thought that captafol was inactivated by reaction with sulfhydryl groups.

Captafol has been found to damage red blood cells by reacting with the sulfhydryl groups residing in the erythrocyte membrane (Kumar et al., 1975). No additional pertinent data regarding the absorption, distribution, metabolism or excretion of captafol were located in the available literature.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of captafol could not be located in the available literature.

5.2. MUTAGENICITY

Captafol consistently caused a base change mutation rather than a frame-shift mutation in bacteria (Moriya et al., 1983; Shirasu, 1975; Shirasu et al., 1976; Ruiz-Vazquez et al., 1978; Kada et al., 1974, 1980; Seiler, 1973). Several abstracts reported the mutagenicity of captafol in bacterial (Nadaska and Jantova, 1979; Zhang et al., 1980), yeast (Turtura and Pozzi-Vincenzi, 1968), silkworm and Drosophila assays (Kawauchi et al., 1979). However, captafol was inactivated by the S-9 liver fractions (Moriya et al., 1976, 1983). Nonenzymatic inactivation appeared to occur in the presence of compounds or materials that contained sulfhydryl groups, such as cysteine and blood (Moriya et al., 1978). The host-mediated assay indicated that captafol did not cause mutation in Salmonella typhimurium after 14 days of treatment with captafol (Kennedy et al., 1975; Legator et al., 1982). However, the U.S. EPA (1983) has invalidated the mouse mutagenicity study done at Industrial Bio-Test Laboratories, which probably is the study published by Kennedy et al. (1975).

In vitro studies with Chinese hamster cells indicated that captafol caused a significant ($p<0.001$) increase in the rate of SCE over the entire dose range tested (2×10^{-6}M-2×10^{-5}M). Only the higher doses (10^{-5}M-2×10^{-5}M) caused chromosome aberrations. Polyploid cells occurred with less significance ($p<0.01$; $p<0.05$) at doses of 2×10^{-6}M and 1×10^{-5}M, respectively (Tezuka et al., 1980). The Chinese (He et al., 1982) reported that captafol caused SCE and chromosomal aberrations in cultivated red

muntjac (Muntiacus muntjak) diploid cells. The study of Rocchi et al. (1980) found that captafol did not induce unscheduled DNA synthesis in human lymphocytes, but their experiments were carried out in media containing serum whose sulfhydryl groups may have inactivated the fungicide. Kennedy et al. (1975) reported that a single i.p. injection of captafol (1.5 or 3.0 mg/kg) given to male mice did not produce any dominant lethal mutations over a 6-week period. However, the total number of implantations appears lower in the captafol-treated group than in controls, but no statistics were performed to determine the level of significance. In another study (Collins, 1972), mean early deaths were significantly higher in the offspring of male Osborne-Mendel rats treated with captafol for 5 days. The effect was more pronounced in rats that received the captafol orally than in those treated with captafol intraperitoneally.

The mutagenicity studies are summarized in Table 5-1.

5.3. TERATOGENICITY

Because of its structural similarity to the known teratogen, thalidomide, the teratogenic potential of captafol has been studied in chick eggs (Verrett et al., 1969), hamsters (Robens, 1970), rabbits (Kennedy et al., 1968), rats (Kennedy et al., 1966, 1968) and non-human primates (Vondruska et al., 1971).

In the study on the development of chickens, captafol was injected into the air space of fertile eggs (20/group) to obtain final concentrations of 18-20, 10-12, 6 and 3 ppm in the egg (Verrett et al., 1969).

When hamsters were given 400 mg/kg of captafol orally on the 7th or 8th day of gestation, 23% (15/61) of fetuses dying late in embryonic life or being born alive had malformations. The malformations consisted of exencephaly (2 cases), fused ribs (8 cases) and short or curved tail (5 cases).

TABLE 5-1

Mutagenicity of Captafol

Assay	Indicator Organism	Strain	Concentration/ Dose	Application Method	Activation System (S-9)	Response	Comments	Reference
Reverse mutation	S. typhimurium	TA1535 TA1536 TA1537 TA1538	200 µg/disk	spot test	+/-	-/-	NC	Carere et al., 1978
Reverse mutation	S. typhimurium	hisG46 TA1530 TA1531 TA1532 TA1534	NR	NR	NR	+ + - - -	NC	Seiler, 1973
Reverse mutation	S. typhimurium	TA98 TA100 TA1535 TA1537 TA1538	5-500 µg/ plate	plate incorporation	+/-	+	Although data were not given for each experiment, captafol was mutagenic at lower dose levels in the absence of S-9 in TA100.	Moriya et al., 1983
Reverse mutation	S. typhimurium	TA1535 TA1536 TA1537 TA1538	50 µg/plate	plate incorporation	NR	-	NC	Shirasu et al., 1976; Shirasu, 1975; Kada et al., 1974, 1980
Reverse mutation	S. typhimurium	SV3	0.1-100 µg/ plate	plate incorporation	NR	+	The purpose of using this unlinked suppressor strain was to detect missense, nonsense, frameshift and deletion mutations in any of at least three genes.	Ruiz-Vazquez et al., 1978
Reverse mutation	E.coli	WP2hcr	0.15 µmole/ plate	plate incorporation	+/-	-/+	The S-9 mixture, as well as rat blood and cysteine, inactivated the mutagenicity of captafol.	Moriya et al., 1978
Reverse mutation	E. coli	WP2hcr	5-500 µg/ plate	plate incorporation	+/-	+	Captafol was mutagenic at lower dose levels in the absence of S-9.	Moriya et al., 1983
Reverse mutation	E. coli	WP2 try hcr$^+$ WP2 try hcr$^-$	50 µg/plate	plate incorporation	-	+	NC	Shirasu et al., 1976; Shirasu, 1975

TABLE 5-1 (cont.)

Assay	Indicator Organism	Strain	Concentration/ Dose	Application Method	Activation System (S-9)	Response	Comments	Reference
Reverse mutation	E. coli	WP2 try hcr$^+$ WP2 try hcr$^-$	10-100 µg/ plate	plate incorporation	NR	+	NC	Kada et al., 1974, 1980
Rec-assay	E. coli	pol A$^+$ pol A$^-$	NR	spot test	+	-	There was no discussion of the effect of S-9 on mutagenicity.	Rosenkranz and Leifer, 1980
Rec-assay	Bacillus subtilis	H17 Rec$^+$ M45 Rec$^-$	0.1 µg/disk	spot test	NR	+	NC	Shirasu et al., 1976; Kada et al., 1980
Point mutation somatic recombination	Aspergillus nidulans	haploid 35	0.2-2000 µg	spot test	NR	-	The result was reported as doubtful.	Bignami et al., 1977
Unscheduled DNA synthesis	human lymphocytes	NR	5 µg/ml	in culture medium	NR	-	Addition of pooled serum and/ or hydroxyurea may inactivate captafol.	Rocchi et al., 1980
Sister chromosome exchange	Chinese hamster cells	NR	2×10^{-4} to 10^{-9} M	in culture medium	NR	+	Results were statistically significant at all dose levels tested ($p<0.001$).	Tezuka et al., 1980
Dominant lethal	rats	Osborne-Mendel	2.5 mg/kg/day 5.0 mg/kg/day 10.0 mg/kg/day	intraperitoneally for 5 days	NA	- - +	A statistically significant ($p<0.05$) increase in the number of mean early deaths/ pregnancy occurred 3 weeks after treatment with the highest dose.	Collins, 1972
			50 mg/kg/day 100 mg/kg/day 200 mg/kg/day	orally for 5 days	NA	- - +	A statistically significant ($p<0.05$) increase in the number of mean early deaths/ pregnancy occurred 1, 2 and 4 weeks after treatment with the highest dose.	
Chromosome aberrations	Chinese hamster cells	NR	2×10^{-4} to 2×10^{-9} M	in culture medium	NR	+	The frequency of chromatid gaps, breaks and exchanges was significantly increased ($p<0.001$) at doses $\geq1\times10^{-9}$ M. The number of polyploid cells also increased.	Tezuka et al., 1980

NR = Not reported

NA = Not applicable

NC = No comment

When a larger dose (500 mg/kg) was given on the 7th or 8th day of gestation, malformations occurred in the cranium (7 cases), the ribs (3 cases) and the limbs (7 cases), but the overall incidence of malformed fetuses was lower (11.4%). At higher doses (600 mg/kg) or at doses (300-500 mg/kg/day) given over 3-5 days, the fetal as well as the maternal mortality rate was very high (>70%), obscuring any teratogenic effect of the fungicide. The animals given captafol orally for >1 day often developed diarrhea. In controls, 0.4% of the embryos had malformations, and the fetal mortality rate was between 2.6 and 4.1% (Robens, 1970) (Table 5-2). In experiments performed at Industrial Bio-Test (IBT) Laboratories, no malformations were observed in New Zealand white rabbits treated orally with captafol in doses ranging from 37.5-150.0 mg/kg from day 6 through day 18 of gestation. Fetal weight and length at birth were reduced by 15-28% in rabbits receiving captafol at a dose of 75 mg/kg or higher. No malformations or decreases in fetal weight and length at birth were seen in Dutch Belted rabbits after the dams ingested 75 mg/kg/day of captafol from day 6 to day 16 of gestation (Kennedy et al., 1968). No malformations were observed in the offspring of rats given captafol (100 mg/kg/day and 500 mg/kg/day) from day 6 to day 15 of gestation (Kennedy et al., 1968) or in the offspring of seven rhesus monkeys fed captafol (6.25-25.0 mg/kg/day) from day 22 to day 32 of gestation (Vondruska et al., 1971).

Several studies performed at IBT Laboratories regarding the teratogenicity of captafol to monkeys, rabbits and rats and reproductive effects in rats have recently been invalidated by the U.S. EPA (1983). It appears that the monkey (Vondruska et al., 1971) and rabbit and rat (Kennedy et al., 1968) teratology studies are among those invalidated by the U.S. EPA (1983), as well as the rat reproductive study (Kennedy, 1966, 1968) discussed in Section 5.4.

TABLE 5-2
Teratogenicity of Captafol in Hamsters[a]

Daily Dose mg/kg/day[b]	Days of Treatment[d]	Maternal Mortality[e]	Fetal Mortality[f]	Malformed Fetuses[g]
500	6-8	3/3	NA	NA
300	6-10	4/5	13/13 (100%)	0
200	6-10	1/8	26/78 (33.3%)	1/52 (1.9%)
100	6-10	2/9	1/74 (1.4%)	1/73 (1.4%)
1000	8	5/5	NA	NA
800	8	4/4	NA	NA
600	7 or 8	11/14	24/33 (72.7%)	0
500	7 or 8	7/20	20/148 (13.5%)	15/132 (11.4%)
400	7 or 8	6/14	32/93 (34.4%)	14/61 (23.0%)
300	7 or 8	4/10	8/67 (11.9%)	1/63 (1.6%)
200	7 or 8	3/18	20/165 (12.1%)	4/148 (2.8%)
100	7 or 8	1/6	2/51 (3.9%)	0
0[c]	7 or 8	0/99	29/1107 (2.6%)	4/1081 (0.4%)
0	NA	0/43	66/1588 (4.1%)	7/1536 (0.4%)

[a]Source: Robens, 1969

[b]Captafol was given orally in CMC which consisted of 0.5 g sodium carboxymethyl cellulose, 0.4 g Tween 60, 0.9 g sodium chloride, 2.0 g benzyl alcohol, and water, q.s. 100 ml.

[c]Vehicle control

[d]The day after mating was considered day 0. All mothers and offspring were evaluated on day 15 of pregnancy.

[e]Maternal mortality indicates the number of dams that died during the experiment per total number of dams undergoing treatment.

[f]Fetal mortality indicates the total number of fetuses dying in utero as well as the number of resorption sites per total number of implantation sites.

[g]Malformed fetuses indicates the number of fetuses with malformations per total number of fetuses born.

NA = Not applicable

In a study on the development of chickens, captafol was injected into the airspace of fertile eggs (20/group) to obtain final concentrations of 18-20, 10-12, 6 and 3 ppm in the egg (Verrett et al., 1969). Of 270 chicks exposed to captafol at all dose levels, 18 had malformations; 5 of these occurred in the head, 7 in the wings, 1 in the leg and 5 in the lower body. The percentage incidence of abnormalities was 6.67% in the captafol-exposed chicks but <2% in the solvent-injected and uninjected controls. No statistical analyses were performed on the data. Micromelia, amelia and phocomelia in the limbs, as well as corneal opacity and defective eyelid formation, were observed in the chicks exposed to captafol. In addition to specific structural abnormalities, there was significant incidence of growth retardation in captafol-treated chicks (Verrett et al., 1969).

5.4. OTHER REPRODUCTIVE EFFECTS

In an unpublished three-generation reproductive study (Kennedy et al., 1966), a reduced lactation index was seen in the F_{1a} generation in rats treated orally with captafol (50 mg/kg/day). At lower doses (2.5-25.0 mg/kg/day), captafol was reported to have no effect (Kennedy et al., 1966). In a published paper, Kennedy et al. (1968) described a three-generation reproductive study in rats fed captafol (50 mg/kg/day). Weight of the offspring at weaning was significantly lower than that of controls in the F_1 and F_3 generations. The decreased weight of the offspring may be related to the decreased lactation index reported in the 1966 paper but denied in the 1968 paper. As mentioned in Section 5.3., this study appears to be one of the IBT studies invalidated by the U.S. EPA (1983).

5.5. SUBCHRONIC AND CHRONIC TOXICITY

Pertinent data regarding the subchronic and chronic toxicity of captafol could not be located in the available literature.

5.6. OTHER RELEVANT INFORMATION

Contact dermatitis has often occurred after exposure to captafol in workers in the timber industry (Stoke, 1979), in Korean orange orchard farmers (Lee et al., 1981) and in Japanese (Shirakawa et al., 1980; Horiuchi and Ando, 1980; Matsushita et al., 1979; Matsushita et al., 1980) and British (Cottel, 1972) farmers. Japanese women appeared more allergic to captafol than Japanese men (Shirakawa et al., 1980). Matsushita et al. (1979) correlated a predisposition to allergic reactions with dietary and respiratory exposure to captafol. Skin patch tests were positive in farmers who used captafol during the previous growing season (Horiuchi and Ando, 1980). Captafol produced delayed hypersensitivity in experimentally exposed mice (Cushman, 1982).

The LD_{50} for rats was given as 6200 mg/kg (Wiswesser, 1976). Because of the structural similarity between captafol and captan, Moriya et al. (1978) implied that the LD_{50} for captafol may be lower in animals on low-protein diets. This effect of low dietary protein may be due to decreased levels of thiols in the gut and other tissue during protein insufficiency (Bridges, 1975).

Captafol has been found to inhibit zoxazolamine hydroxylase activity in rats (Truhaut et al., 1975) and DNA polymerase in isolated bovine liver nuclei (Dillwith and Lewis, 1980).

6. AQUATIC TOXICITY

6.1. ACUTE

Information concerning the acute toxicity of captafol is available for eight freshwater and two marine animal species (Table 6-1). The acute LC_{50} ranged from 17-178 µg/ℓ for five freshwater fish species and from 40-800 µg/ℓfor two freshwater invertebrate species. Tests with marine oysters and killifish yielded respective EC_{50} and LC_{50} values of 34 and 32 µg/ℓ. The LC_{50} or EC_{50} was <59 µg/ℓ for all except two species (goldfish, amphipods). The 96-hour LC_{50} values reported by Johnson and Finley (1980) were measured in soft freshwater (40-50 mg/ℓ hardness as $CaCO_3$). They stated that the acute toxicity of captafol to rainbow trout, goldfish and bluegills was reduced by ~50% in hard freshwater (272 mg/ℓ hardness as $CaCO_3$). They did not provide the LC_{50} values for the species tested in hard water.

6.2. CHRONIC

Pertinent data concerning the chronic toxicity of captafol to aquatic animals could not be located in the literature searched.

6.3. PLANT EFFECTS

The only available information concerning the effects of captafol on aquatic plants was provided by Gangawane and Saler (1979). Captafol was inhibitory to two species of bluegreen alga (Westiellopsis prolifica and Tolypothrix tenuis) at 300 and 500 ppm, respectively. Captafol was stimulatory at 300 ppm to another bluegreen alga (Aulosira fertilissima). Seed germination and root growth of three varieties of rice plant were inhibited at 1000 ppm.

TABLE 6-1

Acute Toxicity of Captafol to Aquatic Animals

Species	Concentration (µg/ℓ)	Effect	Reference
		FRESHWATER	
Amphipod *Gammarus lacustris*	800[a]	96-hour LC_{50}	Johnson and Finley, 1980
Stonefly *Pieronarcys californica*	40[a]	96-hour LC_{50}	Johnson and Finley, 1980
Rainbow trout *Salmo gairdneri*	21[a]	96-hour LC_{50}	Johnson and Finley, 1980
Rainbow trout *S. gairdneri*	27[b]	96-hour LC_{50}	Schneider, 1979
Bluegill *Lepomis macrochirus*	45[b]	96-hour LC_{50}	Schneider, 1979
Bluegill *L. macrochirus*	59[a]	96-hour LC_{50}	Johnson and Finley, 1980
Channel catfish *Ictalurus punctatus*	28[a]	96-hour LC_{50}	Johnson and Finley, 1980
Goldfish *Carassius auratus*	178[a]	96-hour LC_{50}	Johnson and Finley, 1980
Harlequin fish *Rasbora heteromorpha*	17	48-hour LC_{50}	Alabaster, 1969
Zebrafish *Brachydanio rerio*	1000	lethal in 48 minutes	Abedi and Turton, 1968

TABLE 6-1 (cont.)

Species	Concentration (µg/ℓ)	Effect	Reference
		SALTWATER	
Oyster *Crassostrea virginica*	34	96-hour EC_{50} (inhibition of shell growth)	Butler, 1965
Longnose killifish *Fundulus similis*	32	48-hour LC_{50}	Butler, 1965

[a]Wettable powder, 80%

[b]Dust formulation, 97

6.4. RESIDUE

Pertinent data concerning residues of captafol in aquatic organisms could not be located in the literature searched.

6.5. OTHER RELEVANT INFORMATION

Although residue data could not be located, the calculated BCF of captafol in fish is 510 (Kenaga, 1980), indicating that this fungicide has a relatively high bioconcentration potential. This BCF was calculated by Kenaga (1980) by using previously published water solubility data and regression equations. The water solubility of captafol was reported to be 1.4 mg/ℓ. Because the acute LC_{50} for all tested species was 0.8 mg/ℓ or less (see Table 6-1), captafol is toxic to aquatic organisms at concentrations well below its solubility limit.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The U.S. EPA has established the tolerance for captafol in or on raw agricultural products (Code of Federal Regulations, 1982). These tolerances range from 0.1-8 ppm for most fruits and vegetables, while the tolerance for captafol in or on tomatoes is 15 ppm, peaches and apricots is 30 ppm, blueberries is 35 ppm and sour cherries is 50 ppm.

The ACGIH (1980) recommends a TLV of 0.1 mg/m^3 for an 8-hour TWA. No STEL is recommended. The TLV is qualified by the skin designation indicating that significant absorption may occur through exposed cutaneous areas including the eyes and the respiratory mucous membranes, either by direct contact or by inhalation of or exposure to airborne particles. The ACGIH (1983) documentation emphasizes the potential of captafol to cause skin and respiratory sensitization.

7.2. AQUATIC

Existing guidelines or standards for captafol in the aquatic environment could not be located in the literature searched.

8. RISK ASSESSMENT

Studies of the carcinogenicity of captafol could not be located in the available literature. Bacterial assays (Seiler, 1973; Kada et al., 1974; Shirasu, 1975; Shirasu et al., 1976; Ruiz-Vazquez et al., 1978; Moriya et al., 1983) indicate that captafol is a direct acting mutagen. There is evidence that the mutagenic potential of captafol is inactivated by the liver microsomal enzyme system (Moriya et al., 1976, 1983) or by sulfhydryl groups available in the blood or gut (Moriya et al., 1978). In a dominant lethal mutagenicity study, an oral dose of 50 mg/kg/day in male rats produced no effects, while an oral dose of 200 mg/kg/day produced a decreased pregnancy rate and an increased resorption rate (Collins, 1972).

Captafol causes malformations in chickens (Verrett et al., 1969), but its teratogenicity in mammals is equivocal. In a study by Robens (1970), an oral dose of 100 mg/kg of captafol given to hamsters on day 7 or 8 of pregnancy appeared to result in no fetal effects, but the maternal mortality rate increased. At oral doses of 200 and 300 mg/kg, fetal mortality increased, but the percentage of malformed fetuses did not appear higher than the percentage in controls. Oral doses of 400-500 mg/kg resulted in both increased fetal death and increases in the incidence of malformation in the hamster. Tests to determine the level of statistical significance were not performed on Robens's (1970) data. In multiple exposure experiments, 100 mg/kg/day given to hamsters on days 6-10 of pregnancy appeared to produce no fetal effects, although it increased maternal mortality. An oral dose of 200 mg/kg/day on days 6-10 of pregnancy increased fetal mortality but did not increase malformations in surviving fetuses. Oral doses of 300 and 500 mg/kg/day on days 6 to 8 or 10 of pregnancy caused 100% maternal mortality (Robens, 1970).

The teratogenicity studies and the three-generation reproductive study performed at IBT Laboratories (Kennedy et al., 1968, 1966; Vondruska et al., 1971) appear to have been invalidated (U.S. EPA, 1983). Captafol appears to cause hypersensitivity through direct cutaneous contact and through inhalation.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment, however, can be presented in this chapter.

The CBI Appendix to this document reviews other animal data that indicate that captafol is carcinogenic to mice. A q_1^* of 8.55×10^{-3} $(mg/kg/day)^{-1}$ is recommended for use in estimating the increased risk of cancer due to human ingestion of captafol. According to guidelines proposed by the EPA for the assessment of carcinogenic risk, captafol should now be classified in Group C, a possible human carcinogen. This category is used for agents with limited evidence of animal carcinogenicity in the absence of human data. The q_1^* value was calculated from dose-response dat for lymphosarcomas in female mice fed captafol in the diet using the l[illegible]rized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). The conversion factor used to calculate the q_1^* for humans (assuming 70 kg body weight) from animal data was the cube root of the body weight ratio (Federal Register, 1980).

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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